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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,123	10/03/2003	Bernd Klinksiek	Bayer 10261-WCG	2253

27386 7590 06/09/2009

NORRIS, MCLAUGHLIN & MARCUS, P.A.
875 THIRD AVE
18TH FLOOR
NEW YORK, NY 10022

EXAMINER
MAEWALL, SNIGDHA

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
06/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/679,123	KLINKSIEK ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-36,40,42,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-36 and 40, 42 and 44-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of Applicants arguments/remarks and amended claims filed on 03/13/09 are acknowledged.

Claims 1-15 have been withdrawn. Claims 37-39, 41 and 43 have been cancelled.

Claims 16, 24, 26, 29, 34, 40, 42 and 45 have been amended.

Claims **16-36, 40, 42 and 44-45** are under prosecution.

The rejections not reiterated herein have been withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims **16-36, 40, 42 and 44-45** are rejected under 35 U.S.C. 103(a) as being unpatentable over Westesen et al. (US Patent No. 5,885,486) in view of Timothy et al. (Biotechnol. Prog. 200, 16, 402-407, presented in IDS).

Westesen et al. discloses an invention relating to the area of administration forms and delivery systems for drugs, vaccines and other bioactive agents. The reference also describes the process of preparing micron and submicron particles of bioactive agents. The process as depicted describes that a solid lipid or bioactive agent or a mixture of solid lipids is melted, stabilizers are added either to the lipid or bioactive agent and to the aqueous phase only depending on their physicochemical characteristics. Stabilizers may also be added or exchanged after homogenization.

Drugs or bioactive agents can be melted together with lipid. Solid lipid particles such as fatty acids and their esters are disclosed on column 9, lines 23-25. Various drugs have been disclosed in column 10, lines 30-60. The bioactive agents can be dissolved, soulubilized and dispersed in the matrix, see column 10, lines 61-64. The reference teaches that drugs or bioactive substances may be melted or may be dissolved, solubilized or dispersed in the lipid melt, see column 11, step (4). The melted lipid compounds are emulsified in the dispersion medium, see step (5) on column 11. Starch and glucose are taught as stabilizers in column 15, lines 35-38. propylene glycol is taught in column 15, lines 40-45. Glycerol is taught in example 26.

The aqueous phase is heated to the temperature of the melt before mixing and may contain for example, stabilizers, isotonicity agents, buffering substances, and /or preservatives. The molten compounds are emulsified in an aqueous phase by high

pressure homogenization (abstract, column 11 and steps 1-8). Drugs or bioactive agents particularly suitable are listed in column 10, lines 30-60). Ibuprofen and vitamins are also enlisted on the same column. Further in step 8 in column 11, lines 50-55, it is disclosed that the dispersion medium can be reduced by standard techniques such as freeze drying and the lyophilized powder can also be processed into other pharmaceutical formulations such as tablets etc. Regarding the end product being emulsion, the prior art teaches that the melted lipid compounds are emulsified in dispersion medium (see step (5) in column 11 (instant specification , on page 20, teaches in lines 27-28 that the heating step is for very short time such that the emulsion state is present for short time).

The bioactive drugs can be dissolved or crystalline or amorphous or a mixture of these crystallographic states. Role of surfactant is described in example 19 on column 24. Various isotonicity agents such as glycerol or xylitol and sucrose, glucose are disclosed on column 10, lines 10-15. The suspensions and lyophilizates can be used for peroral, buccal, pulmonary etc. depending o n the particle size (see column 14, lines 40-45). The reference further teaches the importance of smaller particle size during drug delivery process (see column 2, lines 10-25). The reference teaches that the drug carrier systems in the micrometer size range are represented as microspheres which are encapsulated (column 3, lines 30-35).

Westesen et al. do not disclose adding compressible fluid in the supercritical state under pressure to the suspension.

Timothy et al. teaches a method for particle size reduction based on rapid expansion from supercritical fluids, especially CO2. Timothy et al. teaches that the pharmacokinetic properties of both oral and injectable formulations are dependent on the particle size. Small particles are often needed in order to maximize surface are, improve bioavailability and for dissolution requirements. Use of surfactant such as tween 80 is described on page 403 for aiding in the stabilization of drug particles.) also see page 405, second paragraph). Micronization of various drugs were assessed at various temperatures and pressures as depicted on page 404 under the heading "results and discussion." Timothy et al. further disclose that the goal was to produce aqueous suspensions of water insoluble drugs by the RESAS of CO2 solutions(page 402, last paragraph).

It would have been obvious to the one of ordinary skilled in the art at the time the invention was made to utilize the compressible fluid in the supercritical state under pressure supercritical fluid such as CO2 as disclosed by Timothy et al. into the process disclosed by Westesen et al. because Westesen et al. also teaches the preparation of micron and submicron particles consisting of poorly water soluble bioactive agents and their use in drug delivery systems. One skilled in the art would have been motivated to prepare pulverulent active substances by utilizing the process of both Westesen et al. and Timothy et al. with a reasonable expectation of success.

Response to Arguments

4. Applicant's arguments filed 03/13/09 have been fully considered but they are not persuasive.

Applicant argues that the combination of the references do not show the exact sequence of the processing steps claimed.

Applicant argues that: The active substance is always incorporated into the lipid melt, prior to contacting said mixture with the dispersion medium. Said contacting may be melting together with the lipid or dissolution, solution or dispersion in a lipid-melt (see col. 11, lines 16-20). From that it should be clear that nothing is "suspended" in an aqueous phase, as melts are liquids and thus cannot be suspended.
Considering, but for purely academic reasons, that such suspending would be feasible with a melt, by misinterpreting "suspending" as of meaning "dispersing" as to the Westesen et al. reference, the distinct sequence of Applicants Claims 16, 26 and 40 is not met by the Westesen et al. reference.

Applicant's arguments are not persuasive because the primary reference teaches that the drugs or bioactive substances may be melted or may be dissolved, solubilized or **dispersed** in the lipid melt, see column 11, step (4). The melted lipid compounds are emulsified in the dispersion medium, see step (5) on column 11. as such, it would have been obvious to one of ordinary skill to either melt the drug before or after the active was suspended in dispersant. Since the process comprises melting step later, it the position of the examiner that this specific step does not change the property of the resulting compound, i.e. the end product. As pointed out before, the sequence of steps does not show any unexpected property associated with the melting step. Additionally, Applicants arguments regarding active substance not being added to an aqueous phase is not persuasive because the primary reference teaches the process of preparing micron and submicron particles of bioactive agents. The process as depicted describes that a solid lipid or bioactive agent or a mixture of solid lipids is melted; stabilizers are added either to the lipid or bioactive agent or to the **aqueous phase only** depending on

their physicochemical characteristics. Therefore, the suspension of active agent with an aqueous solution is also disclosed in the prior art in addition to forming emulsion.

Applicant argues Timothy fails to recite the step of suspending the active agent.

In response to applicant's argument that Timothy fails to recite step of adding active agent to aqueous, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case Timothy has been cited for addition of active to supercritical CO2 gas.

Furthermore, as per MPEP 2144.04:

Ex parte Rubin, 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render *prima facie* obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

In consonant with above, the step of melting the solid active either before or after in the sequence does not alter the property of the end product. As pointed out before, no unexpected result has been shown with respect to the claimed sequence of adding an active and melting it later by heating as shown in step (c) claimed. Wherein the prior

art discloses melting the active followed by heating. The end product is still expected to be similar.

5. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Westesen et al. (US Patent No. 5,885,486) in view of Timothy et al. (Biotechnol. Prog. 200, 16, 402-407) and further in view of Rochling etal. (USP 6,602,823).

The references taught above generically teach additives in the preparation. The references do not teach each and every additive claimed in claim 42. Rochling teaches various specific additives that are known to be utilized in the formulations. Rochling teaches dispersants such as gelatin, starch, polyvinyl alcohol, polyvinylpyrrolidone and preservatives in column 6, lines 50-65. Fillers such as carbonates and silicates silica gels in column 7, lines 1-10.

It would have been obvious to one of ordinary skill in the art to substitute specific additives in formulation of the Westesen and Timothy's teachings motivated by the teachings of Rochling et al.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612